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Inhalation Teratology Studies of Captan and Folpet in Mice

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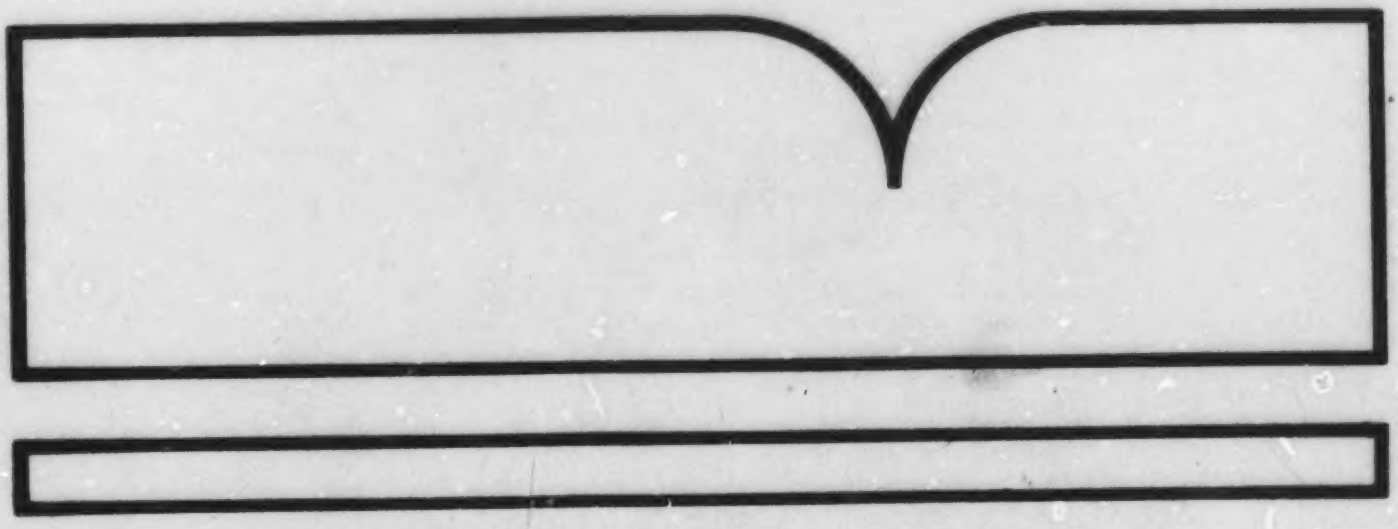

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INHALATION TERATOLOGY STUDIES OF CAPTAN AND FOLPET IN MICE

by

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16. ABSTRACT

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FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our Nation's population.

The complexities of environmental problems originate in the deep interdependent relationships between the various physical and biological segments of man's natural and social world. Solutions to these environmental problems require an integrated program of research and development using input from a number of disciplines. The Health Effects Research Laboratory, Research Triangle Park, NC and Cincinnati, OH conducts a coordinated environmental health research program in toxicology, epidemiology and clinical studies using human volunteer subjects. Wide ranges of pollutants known or suspected to cause health problems are studied. The research focuses on air pollutants, water pollutants, toxic substances, hazardous wastes, pesticides, and non-ionizing radiation. The laboratory participates in the development and revision of air and water quality criteria and health assessment documents on pollutants for which regulatory actions are being considered. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of environmental regulatory decisions involving the protection of the health and welfare of all U.S. inhabitants.

F.Gordon Hueter,Ph.D.
Director
Health Effects Research Laboratory

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Timed pregnant CD-1 mice were exposed to captan or folpet by the intragastric, subcutaneous or inhalation route. A dose of 100 mg/kg/day of captan or folpet was administered subcutaneously or intragastrically from day 6-15 of gestation. The dose levels for the inhalation route were averaged from daily exposure levels determined by monitoring the chambers. The inhalation route provided daily average concentrations approximating 491 mg/m^3 for captan and 624 mg/m^3 for folpet, four hr/day from the 6th to the 13th day of gestation. The particle size was less than 5 μm. There was approximately 10% maternal mortality with both captan and folpet by the inhalation route, while no mortality was seen by the other two routes. The only fetal toxicity noted was a reduction in fetal body weight in the group administered captan subcutaneously. Neither captan nor folpet were teratogenic in CD-1 mice exposed by the subcutaneous, oral or inhalation routes.

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INHALATION TERATOLOGY STUDIES IN MICE*

INTRODUCTION

Captan [N-(trichloromethylthio)-3a,4,7,7a-tetrahydrophthalimide] and folpet [N-(trichloromethyl-thio)phthalimide) are fungicides generally considered to have a low order of toxicity with acute LD-50s in rats in the range of 8-12 g/kg although both compounds have been demonstrated to be mutagenic (1). Both captan and folpet are thalidomido derivatives with folpet having a phthalimide moiety similar to thalidomide while captan is a tetrahydrophthalimide. This similarity to thalidomide generated a number of studies regarding the teratogenic potential of these compounds.

Robens (2) reported that both captan and folpet produced maternal toxicity and lethality following oral treatment to hamsters at doses of 200 to 2500 mg/kg. These doses resulted in the production of many small fetuses although few grossly detectable anomalies were seen. Similarly, captan administration to the C57Bl/6 mouse at dose levels of 100 mg/kg did not produce any malformations by the oral route but did produce some fetal toxicity and malformations by the subcutaneous route. The malformations were of the type that were often observed in the control animals and the effect was not replicated in a second study (3,4). No adverse effects of captan were produced in the AKR strain of mouse by the subcutaneous route at 100 mg/kg (3,4). Captan was found to be not teratogenic in the rhesus monkey after administration by gastric intubation of doses up to 25 mg/kg on gestational days 22-32 (5). Fabro et al.(6) reported that captan was not teratogenic in the New Zealand white rabbit when administered 80 mg/kg on days 7-12 of gestation, but McLaughlin et al. (7) reported in an abstract that captan produced malformations in the same rabbit strain after captan administration on days 6-16 of gestation at a dose of 75 mg/kg. They also studied folpet at the same dose level and found it to be non-teratogenic. In a preliminary study with the Beagle dog, captan was administered at 15, 30, or 60 mg/kg throughout gestation. At the two higher dose levels, stillbirths and malformations were reported (8).

Studies in the chick embryo have shown captan, folpet and the epoxide of captan to have a marked toxic effect at 18 ppm resulting in 74 and 100% mortality respectively. There was also a low level of malformations in the captan and folpet treated chicks but none in those treated with captan epoxide (9). An additional study in chicks by Martin et al. (10)

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*Presented in part at the 17th Annual Meeting of the Society of Toxicology, San Francisco, Calif. March 1978.

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confirmed the teratogenic results from captan and folpet treatment and indicated that they were generally associated with fetal toxicity or mortality. A teratogenic evaluation in snapping turtles indicated that captan had a moderate teratogenic effect (11). Since most of the teratology studies were done using the oral route of administration and since some of the species displayed a teratogenic response, this study was undertaken to evaluate the inhalation route of exposure to captan or folpet using the random bred CD-1 mouse.

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METHODS

Random bred CD-1 mice with known insemination dates were obtained from the Charles River Labs., Inc., Wilmington, Mass. The detection of a vaginal plug denoted day zero of gestation. The mice were weighed on day 6 of gestation and on the day of sacrifice.

Technical grade captan and folpet were used with purities of 86.0% and 87.0% respectively. Solutions of captan or folpet in corn oil:acetone (9:1) were administered intragastrically and solutions in DMSO (dimethyl sulfoxide) were administered subcutaneously. Concurrent control mice were administered the vehicle. The compounds were administered daily from gestational day 6 to 15 using a volume of 0.1 ml/mouse/day. The doses were based on the day 6 body weight.

The dose levels of captan and folpet for both the oral and subcutaneous studies were 100 mg/kg approximating 1/100th of the LD-50 which is 10 g/kg. There were 15-20 mice per group and the mice which were non-pregnant are not included in the tables. The incidence of non-pregnant mice was equivalent in the control and treated groups and was not considered to be compound related. There were 18 mice in each of the air control and captan inhalation groups and 15 mice in each of the air and folpet inhalation groups. Inhalation exposures were for 4 hr/day from day 6-13 of gestation. The number of treatment days was 2 less for the inhalation studies compared to the oral and subcutaneous studies due to maternal mortality. An air control group and captan exposed group were studied concurrently. Following that experiment, an additional air control group and folpet group were studied. Both the treated and control groups were exposed in identical chambers (113 liter plexiglass). Chamber air flow and noise levels were duplicated for the two studies. Captan and folpet, unmilled, were generated into an inhalable dust with particle sizes less than 5 μm using the Farmer Pulse-Puff Dust Generator (12).

All mice were sacrificed on gestational day 17. The maternal liver, gravid uterus and fetuses were removed and weighed. Half of each litter was stored in Bouin's solution until dissected and the remainder in alcohol pending staining with alizarin red S for skeletal examination.

The following conventions were observed in compiling the data. If a fetus was either dead or resorbed, it was regarded as a dead fetus. Only live fetuses were examined for anatomical abnormalities. A fetus was classified abnormal if it was alive and had at least one type of anomaly. The corrected maternal weight was calculated by subtracting the gravid uterus weight from the maternal weight gain on the day of

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sacrifice. This corrected maternal weight was then used to calculate the maternal weight gain by subtracting the day 6 body weight from the corrected maternal sacrifice weight. The maternal liver-to-body weight ratio and the lung-to-body weight ratio were calculated using the corrected maternal weight. Statistical analyses were performed using the student's t and the Mann-Whitney U test. All data are presented using the litter as the unit of calculation. All values are the means ± SEMs.

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RESULTS AND COMMENTS

The inhalation study required the determination of the chamber and particle parameters which are presented in Table 1. The mass median diameter (MMD) was less than 5 μm for both captan and folpet. The mean chamber concentration of both captan and folpet are defined by the means and ranges of the samples that were taken throughout the exposure. The average concentrations of captan and folpet were 491 and 624 mg/m^3, respectively, which are approximately 1/8th the acute LC-50 doses of 4,000 and 6,500 mg/m^3, respectively. By the 13th day of gestation, 4 of the 18 mice exposed to captan had died, indicating that a lethal dose of captan could be absorbed through the lungs. Although the mice were also exposed to the particulate material that collected on their fur in the inhalation chambers, it is quite unlikely that a dose of 10 g/kg was available on the fur for oral consumption. Particles which had collected on the fur during exposure were removed as the mice were taken from the chamber. In the folpet group, 5 mice had died by the fifth exposure. The remaining mice showed labored breathing and loss of hair around the face which was not seen in the control or captan treated mice. The inhalation exposures were stopped after the 13th day of gestation due to toxicity and lethality in both the captan and folpet groups.

The toxicologic evaluation of the maternal mice is presented in Table 2. In the orally dosed groups, there were no significant changes in maternal body weight but there was a significant decrease in the liver-to-body weight ratio of the folpet treated mice. There were no significant changes in the groups treated subcutaneously with either captan or folpet. In the inhalation study, maternal mortality was seen in both groups; i.e. 4 of 18 and 5 of 15 in the captan and folpet groups, respectively. The remainder of the mice not included in the tables were non-pregnant, In addition, the maternal weight gain was significantly reduced in both the captan and folpet inhalation groups; however, there was no effect on the liver-to-body weight ratios. In the captan study, the lung-to-body weight ratios were determined. The captan treated group had a ratio of 0.65 ± 0.03 which was significantly greater ($p < 0.01$) than the ratio of 0.52 ± 0.15 for the air control group.

In general, captan was not toxic in either the oral or subcutaneous study at 100 mg/kg (approximately 1/100th the LD-50) but was toxic and lethal in the inhalation study at 491 mg/m^3 (approximately 1/8th the LC-50). Similarly, folpet was slightly toxic in the oral study; not

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toxic in the subcutaneous study; and very toxic and lethal in the inhalation study. It is not known how the oral and subcutaneous dose levels relate to the inhalation dose level since blood levels or body burdens were not determined.

TABLE 1

Chamber concentrations and aerosol particle characteristics for captan and folpet during 4 hr inhalation exposures of pregnant CD-1 mice on days 6-13 of gestation. Concentrations corrected for percent active ingredient in technical material (86% for captan; 87% for folpet).

Day gestation	Mean chamber conc. (range), mg/m³	Particle Parameters[a]		
		CMD[b]	σG[c]	MMD[d]
Captan				
6	543 (48-1109)	1.48	1.84	4.56
7	533 (202-727)	0.46	2.25	1.97
8	485 (331-787)	0.53	2.11	2.84
9	475 (196-601)	0.56	2.17	3.41
10	503 (248-672)	0.54	2.19	3.38
11	454 (276-819)	0.63	2.00	2.64
12	461 (304-681)	0.56	2.00	2.37
13	476 (294-705)	0.50	2.16	2.96
Folpet				
6	770 (533-908)	0.52	2.00	2.23
7	615 (489-865)	0.57	1.91	2.02
8	646 (437-865)	0.65	1.78	1.85
9	662 (558-848)	0.66	1.67	1.46
10	639 (552-865)	0.67	1.67	1.48
11	690 (375-1031)	0.66	1.62	1.33
12	537 (352-834)	0.70	1.69	1.60
13	490 (352-576)	0.65	1.83	1.92

[a] Average values for samples taken hourly during the 4 hr exposure using the Royco 225 particle monitor; counts analysis consisted of probit-frequency followed by the Hatch-Choate equation.

[b] CMD = count median diameter.

[c] σ = standard error.

[d] MMD = mass median diameter.

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TABLE 2

Parameters of Maternal Toxicity in Captan- and Folpet-treated Pregnant CD-1 Mice.

Compound	Route	Dose mg/kg mg/m³	CD-1 mice no. preg.	Maternal Wt. Gain (g) $\bar{X}$ SE	Liver/Body Wt x 100 $\bar{X}$ SE
CO:Ac[c]	Oral	[a]	8	3.63 ± 0.40	7.22 ± 0.12
Captan	Oral	100	9	3.23 ± 0.65	7.10 ± 0.17
Folpet	Oral	100	8	2.96 ± 0.34	6.61 ± 0.15[b]
DMSO	Subc.	[a]	8	2.92 ± 0.31	7.38 ± 0.28
Captan	Subc.	100	8	2.40 ± 0.65	7.56 ± 0.25
Folpet	Subc.	100	7	3.42 ± 0.34	7.30 ± 0.01
Air	Inhal.	-	12	2.42 ± 0.70	7.10 ± 0.13
Captan	Inhal.	491	6	0.26 ± 1.12[b]	6.76 ± 0.32
Air	Inhal.	-	9	2.62 ± 1.17	6.90 ± 0.43
Folpet	Inhal.	624	7	-0.64 ± 0.82[b]	7.21 ± 0.11

[a] = 0.1 ml/mouse

[b] $p < .05$.

[c] corn oil:acetone (9:1)

The toxicologic evaluation of the fetuses is presented in Table 3. The average number of implantations and live fetuses per litter in the treatment groups did not differ significantly from control values. There was no adverse effect on fetal body weight in the oral treatment mice. However, in the subcutaneous treatment groups, there was a significant decrease in the fetal body weight of the captan group but not in the folpet group. In the inhalation treatment groups, there was a slight but nonsignificant increase in fetal mortality in the captan exposed group. A similar slight increase in fetal mortality was noted in the folpet exposed group and this increase was statistically significant. However, the incidence of fetal mortality in the folpet exposed group was generally in the same range as the other groups both treated and control, and may have no toxicologic significance.

Livers were removed and weighed from three fetuses in each of three litters from the DMSO and captan-subcutaneous groups. These carcasses were then processed for skeletal examination. The corresponding placentas

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Ioxicologic Parameters of Eetuses Erom CD-1 Mice Ireated with Captan or Eolpet

Compound	Route	No. litters	Implants litter X̄ ± SE	Live fetus litter X̄ ± SE	% Eetal mortality X̄ ± SE	Eetal Wt. (g) X̄	SE
CO:Ac[b]	Oral	8	12.4 ± 0.7	10.1 ± 0.7	18.1 ± 4.3	0.94 ± 0.04	
Captan	Oral	9	13.0 ± 0.9	10.2 ± 1.5	19.7 ± 10.5	0.90 ± 0.03	
Eolpet	Oral	8	11.9 ± 1.0	11.0 ± 0.8	6.3 ± 2.7	0.99 ± 0.04	
DMSO	Subc.	8	11.9 ± 1.4	10.4 ± 1.3	14.5 ± 3.2	1.00 ± 0.05	
Captan	Subc.	8	12.8 ± 0.8	10.1 ± 1.0	20.5 ± 6.1	0.86 ± 0.03[a]	
Eolpet	Subc.	7	11.4 ± 1.1	9.7 ± 1.4	17.6 ± 5.9	1.06 ± 0.03	
Air	Inhal.	12	12.4 ± 0.8	11.1 ± 0.9	10.3 ± 5.4	1.19 ± 0.06	
Captan	Inhal.	6	12.7 ± 0.7	10.0 ± 0.9	21.0 ± 6.1	1.07 ± 0.10	
Air	Inhal.	9	10.4 ± 1.3	9.4 ± 1.2	8.9 ± 2.9	1.23 ± 0.06	
Eolpet	Inhal.	7	13.1 ± 0.5	10.6 ± 0.5	19.0 ± 4.0[a]	0.94 ± 0.06	

[a] p = < 05.

[b] CO:Ac = corn oil:acetone (9:1)

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were also weighed. These data are presented in Table 4. There were no statistically significant differences between the DMSO- and captan-exposed fetuses in terms of fetal body weight, fetal liver weight, liver to body weight ratio, placental weight or placenta weight to maternal body weight ratio.

TABLE 4

Fetal Liver Weights and Placental Weights of Captan Mice Treated Subcutaneously.

Compound	DMSO	Captan
No. Litters	3	3
No. Fetuses	9	9
Fetal Body Wt (g)	0.92 ± 0.08	0.94 ± 0.15
Fetal Liver Wt (g)	0.060 ± 0.004	0.066 ± 0.011
Fetal Liver Wt/ Body Wt x 100	6.58 ± 0.21	7.16 ± 0.53
Placenta Wt (g)	0.093 ± 0.004	0.088 ± 0.013
Placenta Wt/ Body Wt x 100	10.48 ± 1.45	8.33 ± 0.1

The fetuses were examined for malformations by dissection for soft tissue anomalies and by alizarin staining for skeletal anomalies. These results are presented in Table 5. The corn oil and DMSO control groups each had one abnormal fetus while none was seen in the oral captan, oral folpet, or the subcutaneous captan group. The subcutaneous folpet group had two abnormal fetuses, e.g. open eye and lung dysgenesis. These incidences are within the normal range for this strain of mouse. In the inhalation groups, the air exposed mice had a few malformations which would not be considered excessive for the procedure. In the captan and folpet inhalation groups, the incidence and type of malformations were comparable to or less than the control groups.

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TABLE 5

Teratologic Observations of Fetuses from CD-1 Mice Exposed to Captan or Folpet During Gestation

Compound	Route	No. fetuses	No. Abnormal fetuses	No. litters with Abnormal fetuses	Anomaly
Corn oil	Oral	81	1	1	Fused ribs
Captan	Oral	91	0	0	-
Folpet	Oral	88	0	0	-
DMSO	Subc.	83	1	1	Digital dysplasia
Captan	Subc.	81	0	0	-
Folpet	Subc.	68	2	2	Open eye, lung dysgenesis
Air	Inhal.	132	4	4	Cleft lip & palate, cleft palate, clubfoot, extra kidney
Captan	Inhal.	60	2	1	Cleft palate (2)
Air	Inhal.	85	1	1	Encephalocoele
Folpet	Inhal.	74	3	3	Cleft palate (2), encephalocoele

Neither captan nor folpet were teratogenic by the oral, subcutaneous or inhalation route of administration. There was some maternal or fetal toxicity in the oral folpet group, captan subcutaneous group, and both captan and folpet inhalation groups. There was no apparent relationship between maternal and fetal toxicity. It appeared that maternal toxicity did not always produce adverse fetal effects although in some situations, it may have contributed to fetal toxicity. Although direct comparisons of dose levels which were administered could be made, it is difficult to make a general comparison of toxicity between the inhalation route and the other two routes until the absorption, distribution and resulting concentration at the target site, namely the fetus, is determined. However, since the inhalation dose levels of 1/8th of the maternal LC-50s produced so few fetal effects, neither captan nor folpet can be considered teratogenic in mice.

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DeBraun et al. (13) reported that in the rat, 50% of an oral dose of captan was excreted within 9 hr but it took 2 days to excrete 50% of an intraperitoneal dose. Captan is metabolized in the gastrointestinal tract as well as by the liver microsomal system (14). Metabolism and distribution of studies of captan or folpet following inhalation exposure have not been performed. The single lactational transfer study reported showed no captan in cow's milk at a detection limit of 0.01 ppm (15).

Although captan and folpet have some similarities to thalidomide, they do not have the teratogenic actions of thalidomide. This was especially evident in the monkey study in which captan and folpet were administered at 5 times the teratogenic dose level of thalidomide and produced no teratogenic or fetotoxic effects (5).

In summary, in the CD-1 mouse, fetal malformations were not produced from the exposure to either captan or folpet by the oral, subcutaneous or inhalation routes and captan and folpet should be considered non-teratogenic in terms of hazard assessment. In the non-mammalian species such as the chick and turtle, captan may be teratogenic. In the mammalian studies cited using other species, very high dose levels were often used and a low incidence of malformations reported usually in conjunction with fetal or maternal lethality. The one exception was the preliminary study in the Beagle dog which needs replication. In sum, captan and folpet are not teratogenic in the CD-1 mouse by oral, subcutaneous or inhalation route of exposure.

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